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- To review current pathogenetic concepts, classification, diagnosis and risk stratification of systemic mastocytosis.
- To review current management of systemic mastocytosis, including an update of investigational therapies

Activity disclosures

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES: A CONTINUING MEDICAL EDUCATION SERIES

Systemic mastocytosis in adults: 2012 Update on diagnosis, risk stratification, and management

Animesh Pardanani*

Disease Overview: **Systemic mastocytosis (SM) results from a clonal proliferation of abnormal mast cells (MC) in one or more extra-cutaneous organs.**
Diagnosis: **The major criterion is presence of multifocal clusters of morphologically abnormal MC in the bone marrow. Minor diagnostic criteria include elevated serum tryptase level, abnormal MC expression of CD25 and/or CD2, and presence of *KIT*D816V.**
Risk Stratification: **The prognostic relevance of the 2008 World Health Organization (WHO) classification of SM has recently been confirmed. Classification of SM patients into indolent (SM), aggressive SM (ASM), SM associated with a clonal non-MC lineage disease (SM-AHNMD) and mast cell leukemia (MCL) subgroups is a useful first step in establishing prognosis.**
Management: **SM treatment is generally palliative. ISM patients have a normal life expectancy and receive symptom-directed therapy; infrequently, cytoreductive therapy may be indicated for refractory symptoms. ASM patients have disease-related organ dysfunction; interferon-α (±corticosteroids) can control dermatological, hematological, gastrointestinal, skeletal, and mediator-release symptoms, but is hampered by poor tolerability. Similarly, cladribine has broad therapeutic activity, with particular utility when rapid MC debulking is indicated; the main toxicity is myelosuppression. Imatinib has a therapeutic role in the presence of an imatinib-sensitive KIT mutation or in *KIT*D816-unmutated patients. Treatment of SM-AHNMD is governed primarily by the non-MC neoplasm; hydroxyurea has modest utility in this setting.**
Investigational Drugs: **Dasatinib's in vitro anti-KITD816V activity has not translated into significant therapeutic activity in most SM patients. In contrast, preliminary data suggest that Midostaurin may produce significant decreases in MC burden in some patients. Am. J. Hematol. 87:402–411, 2012.** © **2012 Wiley Periodicals, Inc.**

Disease Overview and Pathogenesis

Mastocytosis is one of eight subcategories of myeloproliferative neoplasms (MPN) per the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues [1]. It results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells (MC) that accumulate in one or more organ systems. The sine qua non of mastocytosis is the presence of multifocal clusters of abnormal MC, which in contrast to normal MC are variable in appearance, ranging from round to fusiform variants with long, polar cytoplasmic processes, and may display cytoplasmic hypogranularity with uneven distribution of fine granules, as well as atypical nuclei with monocytoid appearance [2–4].

The clinical presentation of mastocytosis is heterogeneous, ranging from skin-limited disease (cutaneous mastocytosis, CM), particularly in pediatric cases where the majority have disease-onset within the first 2 years of life and commonly experience spontaneous regression of skin lesions [5–8], to a more aggressive variant with extra-cutaneous involvement (systemic mastocytosis, SM) that may be associated with multiorgan dysfunction/failure and shortened survival, that is generally seen in adult patients [9].

The WHO document distinguishes the usually *KIT*-mutated SM from a Philadelphia chromosome-negative MPN with hematological features of chronic eosinophilic leukemia associated with splenomegaly, marked elevation of serum vitamin B_{12}, elevation of serum tryptase, and increased bone marrow (BM) MC commonly in scattered or noncohesive clusters [10]. The latter entity is commonly associated with rearrangement of *PDGFRA* (i.e. *FIP1L1-PDGFR*) and less commonly, *PDGFRB* (e.g. *PRKG2-PDGFRB)*, and is sensitive to treatment with imatinib [11–18]. WHO-defined SM is sometimes associated with a clonally-related second myeloid neoplasm [19–22], which is not surprising considering its origin as a stem cell disease with multilineage clonal involvement [23–25]. Conversely, an otherwise well-defined myeloid malignancy, such as myelodysplastic syndrome (MDS) or a non-mast cell disease MPN, might also harbor neoplastic mast cells [26].

Mastocytosis is frequently associated with somatic gain-of-function point mutations within *KIT*. KIT (CD117) is a Type III receptor tyrosine kinase that is characterized by an extracellular domain comprised of five immunoglobulin (Ig)-like subdomains, a hydrophobic transmembrane region, a negative regulatory juxta-membrane intracellular domain, and a cytoplasmic tyrosine kinase domain that is split by a 77-amino acid hydrophilic insert sequence into adenosine triphosphate binding and phosphotransferase domains [27]. KIT is notably expressed by MC, hematopoietic progenitor cells, germ cells, melanocytes, and interstitial cells of Cajal in the gastrointestinal tract and is therefore functionally relevant for normal mast cell development, hematopoiesis, gametogenesis, melanogenesis, and regulation of slow gastric waves [28]. KIT expression is down regulated upon differentiation of hematopoietic progenitors into mature cells

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of all lineages, except mast cells, which retain high levels of cell surface KIT expression. The interaction between KIT and its ligand, stem cell factor (SCF), plays a key role in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival [29].

Gain-of-function somatic mutations in the *KIT* tyrosine kinase domain, particularly the D816V mutation, have been found to occur in a majority of cases of adult SM, irrespective of WHO SM subtype [9,30]. Other less common (<5%) somatic *KIT* mutations identified in adult SM include V560G [31,32], D815K [33], D816Y [30,33–35], insVI815-816 [30], D816F [33,35], D816H [36], and D820G [37]. Recent studies have confirmed that childhood-onset mastocytosis is also clearly clonal in nature, and is associated with germline or acquired activating *KIT* mutations [38–40]. In one study of pediatric CM that screened the entire *KIT* coding sequence for mutations using skin lesional DNA, only 42% of cases harbored missense mutations targeting *KIT*D816; in 44% of cases, genetic alterations (insertions (insFF419), deletions (Δ419), deletion-insertions (Δ417-419insY), internal tandem duplications (ITD SA501-502, ITD AY502-503, ITD NFAF505-508), and missense mutations (D816V, D816Y, D816I, C443Y, S476I, K509I, D572A, M541L)) were found to mainly involve exons 8 and 9, which encode the fifth Ig (D5) domain and the extracellular region near the transmembrane domain, regions that have previously been shown to be affected in core-binding factor-acute myeloid leukemia (CBF-AML) and in gastrointestinal stromal tumors (GISTs), respectively [41,42]. The aforementioned mutations in the exons 8 and 9 have rarely been described in pediatric or adult mastocytosis, although individual mutations have been reported in CBF-AML (Δ417-419insY) [41,43], kindreds with familial GISTs and mastocytosis (Δ 419) [44], familial mastocytosis (K509I) [45], and GISTs (ITD AY502-503) [42]. As with *KIT*D816V, every one of the mutations in exons 8 and 9 that was tested was found to constitutively activate KIT kinase activity. Other rare germline *KIT* mutations that target the transmembrane domain and that are associated with familial mastocytosis include F522C and A533D [46,47].

While activating *KIT* mutations are frequently associated with human mastocytosis, they do not occur universally, and the question as to whether individual mutations are necessary and sufficient to cause mast cell transformation and whether such mutations alone explain the diverse clinical presentations of mastocytosis remains currently unsettled. Furthermore, while childhood- and adult-onset mastocytosis are both associated with activating *KIT* mutations, the natural history of the two conditions is quite different, with the former often exhibiting skin-limited disease that spontaneously regresses with age; in contrast, the latter is characterized by persistent multiorgan involvement, often with second non-MC hematologic neoplasm.

Experimental data with regard to this issue have not been conclusive; in transgenic mice expressing human *KIT*D816V in mature MC (under the control of the chymase promoter), only a subset (30%) of mice developed a limited form of mastocytosis (some with cutaneous-limited disease) at an old age (12–18 months) [48]. Although BM-derived MC from the transgenic animals eventually became growth factor independent and could be maintained in long-term cultures, the incomplete disease penetrance in this model suggested that additional somatic mutations are necessary for full MC transformation. In another transgenic mouse model that allowed conditional expression of murine *KIT*D814V (the homolog of human *KIT*D816V) driven by the *KIT* promoter, expression of mutant KIT in adult mice including in hematopoietic precursors caused severe mastocytosis with 100% penetrance at a young age [49]. Approximately half of the mice developed a non-MC lineage hematologic neoplasm, most frequently a leukemic disease derived from an immature B-cell precursor. The mice also developed a severe focal inflammatory colitis associated with a massive increase in mucosal mast cell numbers. In contrast, when mutant KIT expression in this model was limited to more mature MC, disease expression was significantly attenuated; while half of the mice developed MC tumors and erosive skin lesions and all developed severe colitis, the disease occurred significantly later and progressed much slower. While both the aforementioned transgenic murine models are imperfect (abnormal intracellular processing/trafficking of human KITD816V resulting in low oncogenicity in the former, and low transgene expression in the latter), they cumulatively suggest that the effects of constitutive KIT signaling depend on the developmental stage of the cell targeted by the gain-of-function mutation. As has been noted in mastocytosis patients [30], mutations targeting undifferentiated progenitors result in multilineage involvement and expression of a severe systemic disease phenotype; in contrast, mutations that target committed MC progenitors or mature MC result in milder forms of the disease.

Other oncogenic mutations recently identified in mastocytosis patients include those in *TET2* (*TET* oncogene family member 2) and *N-RAS* [50,51]. These mutations are not specific to mastocytosis and their pathogenetic role and/or prognostic impact is currently uncertain. *TET2* is a putative tumor suppressor gene; in one study, mutational frequency in SM was 29% and the presence of *TET2* mutations was associated with monocytosis. Further, *TET2* mutations cosegregated with *KIT*D816V but did not appear to affect survival in SM. Interestingly, expression of an activated M-RAS mutant (Q71L) in primary murine BM cells reproducibly generated a lethal mastocytosis and mast cell leukemia (MCL); in contrast, expression of constitutively activated H-RAS (G21V) produced a lethal histiocytic/monocytic leukemia, presumably reflecting significant differences in downstream signaling pathways in these disease models [52].

Diagnosis

The diagnosis of mastocytosis is based on identification of neoplastic MC by morphological, immunophenotypic, and/or genetic (molecular) criteria using well-established criteria as outlined by the 2008 WHO document (Fig. 1) [1]. Biopsy of organs other than BM, such as liver or spleen, is infrequently pursued, either for diagnostic purposes or to demonstrate MC infiltration as the cause of impaired organ dysfunction.

Bone marrow histology

In practice, the current diagnostic approach for SM starts with a BM examination since this site is almost universally involved in adult mastocytosis, and histological diagnostic criteria for non-BM, extracutaneous organ involvement in SM have not been firmly established or widely accepted as of yet. Further, BM examination also allows detection of a second hematologic neoplasm, if present [19,21].

In general, the pathognomonic multifocal dense MC aggregates, frequently in perivascular and/or paratrabecular BM locations (major diagnostic criterion; Fig. 1), may not be readily recognized by standard dyes such as Giemsa, particularly when MC exhibit significant hypogranulation or abnormal nuclear morphology, or in cases with extensive BM involvement by a second hematological neoplasm (e.g., acute myeloid leukemia), or when significant reticulin fibrosis is present. Among the immunohistochemical markers, tryptase is the most sensitive, given that virtually all MC, irrespective of their stage of maturation, activation status, or tissue of localization express this marker, and consequently allows for detection of even small and/or immature MC

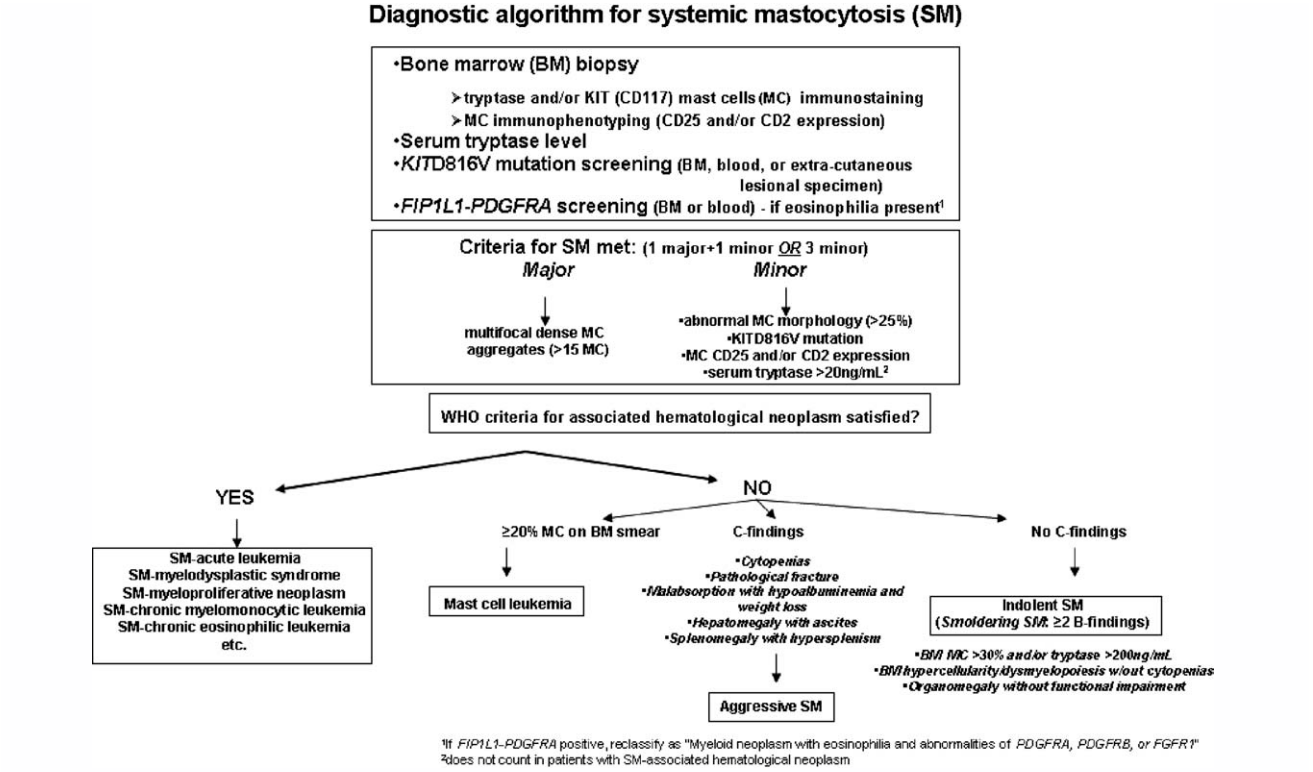

Figure 1. Diganostic algorithm for systemic mastocytosis (SM).

infiltrates [53–55]. It must be emphasized, however, that neither tryptase nor KIT/CD117 immunostaining is able to distinguish between normal and neoplastic MC [56]. Also, abnormal basophils seen in some cases of acute and chronic basophilic leukemia, as well as in chronic myeloid leukemia (CML), and blasts in some AML cases may be tryptase positive, and may prove difficult to distinguish from MC [19].

In contrast, immunohistochemical detection of aberrant CD25 expression on bone marrow MC appears to be a reliable diagnostic tool in SM, given its ability to detect abnormal MC in all SM subtypes, including the rare cases with a loosely scattered, interstitial pattern of MC involvement (see below) [55].

CD30 (Ki-1 antigen) has been reported to be preferentially expressed (proportion of cells as well as intensity of staining) in neoplastic MC from patients with ASM or MCL (11 of 13; 85%) as compared to ISM (12 of 45; 27%) [57]. In the latter group, CD30 expression was significantly correlated with serum tryptase level $\geq$50 ng/mL. The clinical implications of this finding are currently unclear given lack of independent confirmation of this relatively subjective assessment, small number of cases studied (particularly ASM/MCL) and overlap of CD30 expression between ISM and ASM/MCL (e.g. SSM cases were uniformly CD30-positive).

Mast cell immunophenotyping

Neoplastic MC generally express CD25 and/or CD2, and the abnormal expression of at least one of these two antigens counts as a minor criterion toward the diagnosis of SM per the WHO system (Fig. 1) [1]. Expression of CD2 on MC, as assessed by either flow cytometry or immunostaining, has been noted to be variable in SM, and consequently, CD25 expression may be more reliable marker for neoplastic MC [58,59]. The aforementioned immunostaining and immunophenotyping studies enhance the morphological and immunophenotypic distinction between normal (round and CD25-negative) and abnormal (spindle-shaped and CD25-positive) mast cells, respectively [54,59].

Serum tryptase level

Normal MC display a spectrum of 'activation levels' in vivo, and the mechanisms governing the secretory phenotype and mediator release patterns are not completely understood [60]. In SM, an elevated serum tryptase level ($>$20 ng/mL) counts as a minor diagnostic criterion per the WHO framework (Fig. 1) [1], while the levels vary widely, serum tryptase is elevated in the majority of SM patients across all WHO subgroups; a significantly greater proportion of ASM and SM-AHNMD patients exhibit a markedly elevated serum tryptase level ($>$200 ng/mL) compared with those with ISM [9]. Serum tryptase levels are also elevated in a significant proportion of cases with AML, CML, and MDS [61]; consequently, this test has limited diagnostic utility in the presence of a second SM-associated myeloid neoplasm. The correlation between MC mediator levels and presence of MC mediator-release symptoms (MCMRS) or systemic MC burden remains incompletely understood; in one study of indolent mastocytosis patients, MC mediator levels were significantly correlated with BM MC burden, but not MCMRS [62].

Molecular studies

Identification of *KIT*D816V counts as a minor diagnostic criterion per the WHO system (Fig. 1) [1]. Of note, there is a high correlation between *KIT* mutation detection and the proportion of lesional cells in the sample, as well as the sensitivity of the screening method employed [63]. Sensitivity of detection may be enhanced by enriching lesional MC by laser capture microdissection, or magnetic bead- or FACS-based cell sorting, respectively [20,30,64], or through the use of highly sensitive PCR techniques [33]. Outside of a research setting, it is currently not standard practice to screen for *KIT* mutations other than those involving D816. The frequency of involvement of non-MC lineages (generally myeloid, but occasionally lymphoid lineages) by *KIT*D816V appears to be greater in cases of ASM or MCL, as compared with ISM [30]. In contrast, *KIT*D816V is

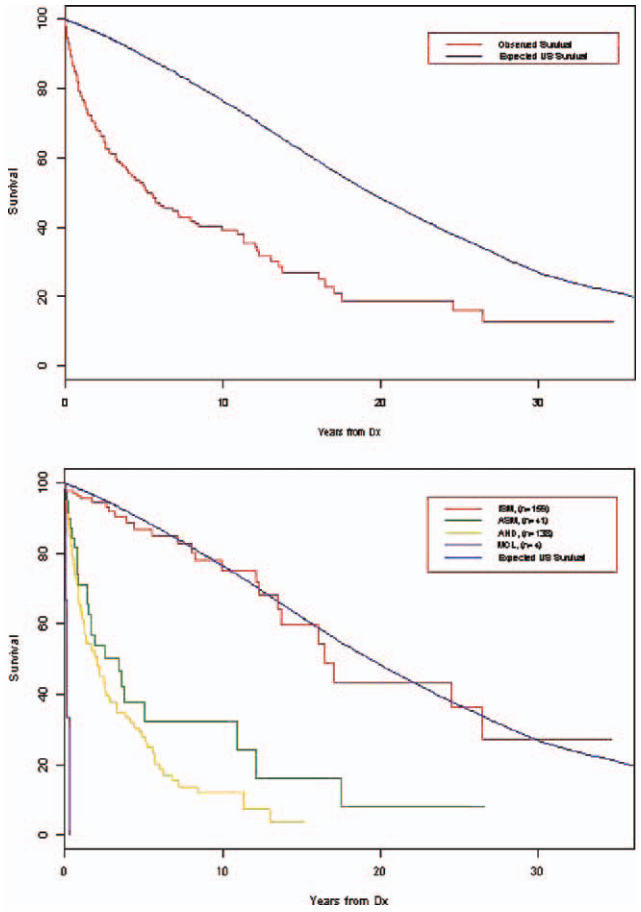

Figure 2. Survival of systemic mastocytosis patients. (A) The observed Kaplan-Meier survival for systemic mastocytosis patients (red) compared with the expected age- and sex-matched US population's survival (blue). (B) The observed Kaplan-Meier survival for systemic mastocytosis patients classified by disease type ISM (red), ASM (green), AHNMD (gold), and MCL (violet) compared with the expected age- and sex-matched US population's survival (blue) for the entire cohort. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

variably present in cells representing the second hematological neoplasm in SM-AHNMD cases, depending upon the particular AHNMD subtype (CMML > MPN, AML > lymphoid neoplasms) [65].

It is important to recognize that rare SM cases may exhibit a well-differentiated phenotype (i.e. relatively normal BM MC morphology; absence of aberrant MC CD25/CD2 expression); these cases are associated with non-D816V *KIT* mutations (e.g. germline F522C or somatic I817V) and, in the case of *KIT*F522C-associated SM, has been shown to be sensitive to imatinib therapy [30,46].

In the presence of blood eosinophilia, screening for *FIP1L1-PDGFRA*, using either FISH or RT-PCR, is warranted [16]. In contrast, conventional cytogenetics analysis generally permits identification of cases of BM mastocytosis associated with a *PDGFRB* rearrangement (i.e. chromosomal translocations involving 5q31-32) [18]. These cases with *PDGFRA/PDGFRB*-rearranged MPN with BM MC hyperplasia are appropriately classified as "Myeloid or lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*" per the WHO classification [10].

Risk Stratification

This section focuses on adult SM patients; their life expectancy, when considered as a group, appears to be shorter as compared with age- and gender-matched controls, with the excess deaths in this group occurring within the first 3 to 5 years after diagnosis (Fig. 2A) [9,66].

The categorization of adult SM patients per the 2008 WHO classification system remains the most practical first step in risk stratifying newly diagnosed patients [1]. The WHO classification recognizes several categories of mastocytosis including (i) cutaneous mastocytosis (limited to the skin; variants include urticaria pigmentosa, diffuse cutaneous mastocytosis and solitary mastocytoma of the skin), (ii) extracutaneous mastocytoma (unifocal nondestructive mast cell tumor with low-grade cellular atypia), (iii) mast cell sarcoma (destructive unifocal mast cell tumor with poorly differentiated mast cells, and tendency to metastasize and/or evolve into MCL), and (iv) SM. The latter is subclassified into four subcategories: indolent SM (ISM; no evidence of extracutaneous organ dysfunction), aggressive SM (ASM; presence of extracutaneous organ dysfunction), SM associated with another clonal hematological non-MC lineage disease (SM-AHNMD), and mast cell leukemia (MCL).

A recent study of 342 adult patients validated, for the first time, the prognostic value of the WHO classification for SM [9].

Indolent SM

In the aforementioned series, ISM comprised the largest subgroup (n = 159; 46%) [9]. Compared with patients with ASM and SM-AHNMD, ISM patients were significantly younger at presentation (median age 49 years) and had a higher prevalence (66%–75%) of UP-like skin lesions, MCMRS and gastrointestinal symptoms; ISM patients were significantly less likely, however, to exhibit constitutional symptoms or hepatosplenomegaly (<20%).

The WHO system recognizes two provisional ISM subvariants: smoldering SM (SSM) and isolated bone marrow (BM) mastocytosis (BMM) [1]. SSM is characterized by a higher burden of MC defined by the presence of ≥2 "B-findings" (Fig. 1). Of the 159 ISM patients in the aforementioned series, 22 (14%) had SSM, 36 (23%) BMM, and the remaining 101 (63%) did not fit in with either category (ISM-other) [62]. SSM patients were significantly older (median age 64 years) than patients with BMM or ISM-other and more frequently presented with constitutional symptoms (45%), anemia (55%), and elevated MC mediator levels. In contrast, BMM patients more frequently presented with MCMRS (86%), including anaphylaxis (78%). Overall median survival in ISM was 198 months, which was not significantly different than that of the age- and sex-matched U.S. control population (Fig. 2B, red curve). SSM patients had a significantly inferior survival (median 120 months) as compared with those with ISM-other (median 301 months) or BMM (not reached).

In a multivariable analysis, advanced age was the primary determinant of inferior survival and accounted for the marked difference in survival between SSM and the other two groups. The overall risk of transformation to acute leukemia or ASM was low (<1% and 3%, respectively) but was significantly higher in SSM (18%). Another recent study confirmed the low-rate of disease progression in ISM; after a median follow-up of 147 months (range, 61–329), the progression rate was 3%; predictors of disease progression were serum β2-microglobulin level and multilineage presence of *KIT*D816V [67].

Systemic mastocytosis with associated clonal hematological nonmast cell lineage disease

SM-AHNMD was the second most common SM subgroup (n = 138; 40%) in the aforementioned series [9,22]. Of these, 123 (89%) had an associated myeloid neoplasm, while the remainder had lymphoma (n = 7), myeloma (n = 5), chronic lymphocytic leukemia (n = 2), or primary

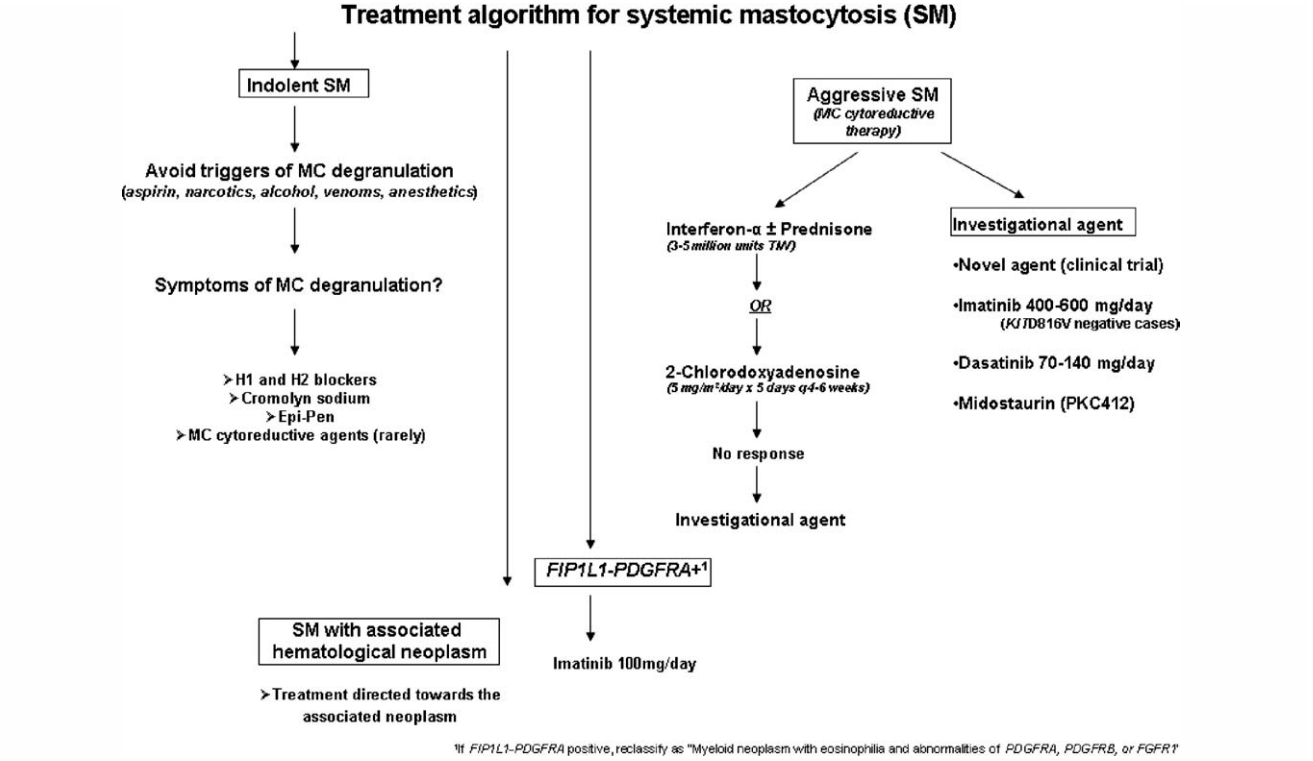

Figure 3. Treatment algorithm for systemic mastocytosis (SM).

amyloidosis ($n = 1$). Of the patients with an associated myeloid malignancy, 55 (45%) had SM-MPN, 36 (29%) SM-chronic myelomonocytic leukemia (SM-CMML), and 28 (23%) SM-MDS. A significant proportion ($n = 42$; 34%) exhibited prominent eosinophilia ($\geq 1.5 \times 10^9$/L), especially those with SM-MPN ($n = 31$; 56%); of the latter, 12 (39%) harbored the *FIP1L1-PDGFRA* fusion.

Overall median survival in SM-AHNMD was 24 months (Fig. 2B, gold curve). SM-MPN patients had a significantly longer median survival (31 months) as compared with patients with SM-CMML (15 months), SM-MDS (13 months), or SM-AL (11 months). Leukemic transformation (13% overall) was seen significantly more frequently in SM-MDS (29%), as compared with SM-MPN (11%) or SM-CMML (6%). Clinical outcome was similar between SM-MPN patients with or without eosinophilia.

Aggressive systemic mastocytosis

ASM was the third most common subgroup ($n = 41$; 12%) in the aforementioned series [9]. ASM patients frequently displayed constitutional symptoms (60%), hepatosplenomegaly (50%), lymphadenopathy (30%), severe anemia (Hgb < 10 g/dL; 24%) or thrombocytopenia (platelets $<100 \times 10^9$/L; 27%), leukocytosis (41%), and markedly elevated serum tryptase levels (>200 ng/mL; 40%). Overall median survival in ASM was 41 months (Fig. 2B, green curve) and leukemic transformation occurred in two patients (5%).

Mast cell leukemia

MCL was relatively rare ($n = 4$; 1%) in the aforementioned series [9]; the prognosis in these cases was dismal with median survival of only 2 months (Fig. 2B, violet curve).

In addition to WHO SM subtype, multivariable analysis shown a significant and independent association between inferior survival and advanced age ($P < 0.0001$), history of weight loss ($P = 0.01$), anemia ($P = 0.007$), thrombocytopenia ($P = 0.0008$), hypoalbuminemia ($P = 0.0008$), and excess BM blasts (>5%; $P = 0.004$) [9].

Peripheral blood immunophenotyping has revealed the presence of circulating CD34-/KIT+ precursor mast cells in SM patients; circulating levels correlated with advanced SM (SM-AHNMD > ASM > ISM), albeit with overlap between subgroups [68]. Further, in a small number of cases, the level of circulating precursor mast cells correlated with effectiveness of MC cytoreductive therapy and with clinical disease relapse, thereby pointing to the potential future utility of such testing.

*KIT*D816V, which is the hallmark of adult SM, has been shown to occur in BM hematopoietic cell compartments other than MC, particularly in cases of SM-AHNMD, ASM, and MCL, but less frequently in ISM, thereby indicating involvement of a pluripotent stem cell in such cases [30]. Further, comprehensive immunophenotyping has shown that an immature BM MC phenotype ($CD25^+/Fc\epsilon RI^{lo}/FSC^{lo}/SSC^{lo}/CD45^{lo}$), in the absence of coexisting normal MC in the BM, correlated with multilineage hematopoietic involvement by *KIT*D816V, regardless of the WHO SM subtype [69]. In contrast, BM MC from patients with ISM subtypes displayed a mature activated MC phenotype (e.g. increased expression of MC activation markers CD63, CD69, and CD203c in patients with BMM) [70]. While such assays require considerable technical expertise, and consequently are not routinely available, these data indicate the prognostic value of the aforementioned observations; in one study, multilineage *KIT*D816V involvement was the most important prognostic criterion for progression of ISM to more aggressive SM subtypes [67].

Treatment

While treatment of adult SM is highly individualized, it is guided only to a limited extent by the presence or absence of a particular molecular abnormality. In general, treatment with small-molecule kinase inhibitors has yielded only modest clinical benefits, likely due to yet unrecognized complexities in the molecular pathogenesis of SM, redundancies in cellular signaling pathways and/or ineffectiveness of

currently available in vivo KITD816V-inhibitors. For the rare SM patient with a transmembrane KIT mutation (e.g., F522C or K509I), dramatic clinical responses to imatinib therapy can be observed [45,46]. Overall, however, although progress has been achieved with some of the newer investigational agents (e.g., midostaurin/PKC412), the promise of truly "targeted therapy" in the vast majority of SM patients (akin to imatinib therapy in CML) has yet to be realized. Drug therapy has not been shown to favorably affect survival in SM and the experience with allogeneic stem cell transplantation is too limited to comment on [71]. Therefore, current therapy in WHO-defined SM is largely palliative and directed at MC degranulation symptoms (e.g. pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks), symptomatic skin disease (e.g. urticaria pigmentosa), and/or organ dysfunction from MC tissue infiltration (e.g. hypersplenism or pathologic fracture). Treatment options in SM range from observation alone (supplemented by preventative measures to avoid precipitating MCMRS), to symptom management (e.g. managing pruritus or diarrhea), to supportive measures (e.g. red blood cell transfusion or osteoporosis treatment), to cytoreductive therapy for MC debulking in the setting of aggressive, advanced, or treatment-refractory disease. An additional challenge in SM treatment is the cumbersome nature of the current treatment response criteria [72], which makes it difficult to compare efficacy of a given treatment across different centers. In this regard, alternative criteria that are more objective, reproducible, and SM-subtype specific as compared with the current criteria have recently been proposed, albeit not yet validated [73].

Currently used agents for SM therapy are presented below. Our current algorithm for SM treatment is illustrated in Fig. 3.

1. Interferon (IFN)-α*:* IFN-α is often considered the first-line cytoreductive therapy in symptomatic SM; since the initial report in 1992 [74], several case reports or small series have shown IFN-α (IFN-α2b in most instances) to improve symptoms of MC degranulation, decrease bone marrow MC infiltration, and ameliorate mastocytosis-related ascites/hepatosplenomegaly, cytopenias, skin findings, and osteoporosis [75–87]. IFN-α treatment is not uniformly effective [88], and the frequency of major response (i.e. complete resolution of one or more baseline "C" findings) is approximately 20 to 30%; the optimal dose and duration of IFN-α therapy for SM remain unclear, however, concurrent administration of corticosteroids (prednisone) may improve its efficacy (up to 40% major response rate) and tolerability [82,89]. The time to best response may be a year or longer [82] and delayed responses to therapy have been described [90]. IFN-α treatment is frequently (up to 50%) complicated by toxicities, including flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism; consequently, the adverse dropout rate with IFN-α treatment is not trivial [82,91,92]. Finally, a significant proportion of patients will relapse within a short period of IFN-α treatment being discontinued, illustrating the cytostatic rather than cytolytic effects of the drug [92].
   In a French study, 20 SM patients (16 ASM and 4 ISM) were treated with IFN-α starting at 1 MU/day with progressive increase to 5 MU/m^2/day; 13 patients were treated for at least 6 months (median dose 3.2 MU/day) [92]. All 13 patients exhibited responses (non were complete) in systemic and cutaneous disease manifestations that were associated with decrease in circulating MC mediator levels, but not in BM MC burden. Adverse effects were frequent (cytopenias and depression in nine and seven patients, respectively); there were two deaths during the treatment phase. Four responding patients experienced prompt relapse of symptoms after treatment cessation.
   In the Mayo Clinic study, 47 patients received IFN-α with or without prednisone [91]; the median weekly dose was 15 MU per week (range 3.5–30 MU per week) and the initial dose of prednisone ranged from 20 mg to 60 mg per day with a slow tapering over weeks or months in some patients. In 40 evaluable patients, the overall response rate (ORR) was 53% (ISM and ASM 60%; SM-AHNMD 45%). Overall median duration of response was 12 months (range, 1–67 months). Responses were not significantly different when comparing patients who did and did not receive prednisone. Absence of systemic mediator-related symptoms was significantly associated with inferior response to IFN-α; 41% versus 77%, respectively. Major toxicities included fatigue, depression and thrombocytopenia.
   Summary: IFN-α has activity in all SM subcategories and has been shown to improve dermatological, hematological, gastrointestinal, and systemic symptoms associated with histamine release. IFN-α also has a role in treating skeletal symptoms because of its ability to increase bone density. Use of higher doses of IFN-α has the potential to decrease the BM MC burden in some patients. We commonly start treatment at the dose of 1 to 3 million units (MU) subcutaneously three times per week, followed by gradual escalation to 3 to 5 MU three to five times per week, if tolerated. Prednisone (30–60 mg/day) is commonly added at the start of treatment to improve tolerability and response, and is tapered over a 2- to 3-month period. IFN-α treatment is generally continued as long as a response is observed and there are no intolerable adverse effects.
2. Cladribine or 2-chlorodeoxyadenosine (2-CdA) has demonstrated in vitro and in vivo activity against neoplastic MC; the published experience suggests that 2-CdA has therapeutic activity in all SM subtypes including in MCL [93–98].
   In the Mayo Clinic study, 2-CdA was administered to 26 patients (eight as first-line); the dose was 5 mg/m^2 per day or 0.13 to 0.17 mg/kg per day for 5 days as a 2-hr intravenous (IV) infusion, and median number of treatment cycles was 3 (range 1–9) [91]. Treatment response was evaluable in 22 patients and the ORR was 55% (ORR in ISM, ASM, and SM-AHNMD was 56%, 50%, and 55%, respectively). Median duration of response was 11 months (range, 3–74 months). Presence of circulating immature myeloid cells was significantly associated with inferior response to 2-CdA (0% vs. 75%). Major toxicities were myelosuppression and infection.
   In a recent French study, 44 patients with mastocytosis were treated with 2-CdA (CM = 3, ISM = 19, SSM = 3, ASM = 12, SM-AHNMD = 6 and MCL = 1) [99]. All patients had failed previous symptomatic therapy and/or IFN-α (n = 10) or kinase inhibitors (n = 7); 2-CdA was given at 0.15 mg/kg/day in a 2-hr infusion or subcutaneously for 5 days, repeated every 1 to 2 months, for a median of four cycles. After a median follow-up of 35 months, no opportunistic infections were seen with the exception of zoster infection in two patients. Responses occurred in 24 of 31 patients with urticaria pigmentosa, 17 of 35 with fatigue, 14 of 24 with flushing, 9 of 24 with pruritus, 9 of 21 with abdominal pain, 1 of 9 with ascites, 11 of

23 with diarrhea, 8 of16 with weight loss, 4 of 14 with headache, 5 of 10 with cough, 7 of 20 with splenomegaly, 2 of 6 with lymphadenopathy, 0 of 2 with pleural effusions, and 5 of 19 with neuropsychological symptoms. In addition, eosinophil count normalized in 7 of 10 cases and a substantial decrease in tryptase levels was also noted. Overall, major (MR) and partial (PR) responses were observed in 7 of 12 patients with ASM, 3 of 3 SSM, 17 of 19 ISM, 2 of 3 CM but in none of the patients with SM-AHNMD. Median duration of response was approximately 20 months.

Summary: The 2-CdA has activity in all SM subtypes. We use 2-CdA as first-line treatment in cases where rapid MC debulking is indicated, or in symptomatic patients who are refractory or intolerant to IFN-α. Potential toxicities of 2-CdA include myelosuppression and lymphopenia with increased risk of opportunistic infections. The limited activity of 2-CdA in SM-AHNMD patients noted in the French study is discrepant with published data; the discrepancy may relate to alternative interpretation of the treatment response data and needs to be confirmed.

3. *Imatinib mesylate (IM)* demonstrates in vitro efficacy against wild-type KIT and certain transmembrane (F522C) and juxta-membrane (V560G) KIT mutants, but not the common kinase (D816V) domain mutants [46,100–102]. Similarly, not all juxta-membrane mutations may be sensitive to IM (e.g. V559I) [103].

   In the Mayo Clinic study that excluded *FIP1L1-PDGFRA*-positive cases, IM was administered to 27 SM patients; the median starting dose was 400 mg per day (range 100–400 mg/day), and the maintenance dose in responding patients ranged from 200 mg/day to 400 mg/day [91]. In 22 evaluable patients, the ORR was 18% (ORR in ISM, ASM, and SM-AHNMD was 14%, 50%, and 9%, respectively), and median duration of response was 19.6 months (range, 9–69 months). Responses included improvement in UP and decrease in the BM MC burden. The majority (86%) of IM-treated patients were *KIT*D816V positive—ORR in mutation-positive and -negative patients was 17% and 33%, respectively. None of the six patients with SM and associated eosinophilia (all *KIT*D816V-positive) responded to IM treatment. Major toxicities included diarrhea and peripheral edema; two patients developed interstitial pneumonitis.

   Data from another study, however, suggested an ORR of 36% in *KIT*D816V-positive SM patients [104]. In yet another study of 20 SM patients treated with IM, only one *KIT*D816V-negative patient responded while six other patients reported symptomatic improvement [105]. Finally, in another study wherein 17 SM patients received IM treatment, the response rate was 29% (one complete and four partial remissions), all in *KIT*D816V-negative patients [106].

   Summary: While IM is the only SM treatment currently approved by the Food and Drug Administration (FDA) (specific indication is treatment of adult patients with ASM without the KITD816V mutation or with unknown KIT mutational status), it has a limited role in the treatment of unselected SM patients, the majority of whom likely harbor KITD816V. The rare SM cases that harbor an IM-sensitive KIT mutation, or those that are KITD816-unmutated may be appropriate candidates for IM treatment.

4. Hydroxyurea (HU): In the Mayo Clinic study, HU was given to 30 SM patients (28 with SM-AHNMD) [91]. The drug was used as first-line therapy in 24 patients. The dose ranged from 500 mg every other day to 2000 mg per day. Treatment response was evaluable in 26 patients; control of thrombocytosis, leukocytosis, and/or hepatosplenomegaly was observed in five SM-AHNMD patients (ORR = 19%). Median duration of response was 31.5 months (range, 5–50 months) and the major toxicity was myelosuppression.

   Summary: The utility of HU in treating SM-AHNMD stems from its myelosuppressive activity. HU does not, however, exhibit any substantial anti-MC effect.

1. Investigational agents:

   (i) Dasatinib has shown efficacy in vitro against various KIT mutants including D816V [107,108]. Furthermore, dasatinib may synergize with PKC412 and chemotherapy in this regard [109–111]. In the largest study of dasatinib therapy in SM [112], the drug was given at a starting dose of 70 mg PO bid to 33 SM patients: 18 ISM, 9 ASM, and 6 with SM-AHNMD. Two (6%) patients, both of whom were D816V-negative, achieved complete remission. Nine (27%) patients experienced symptomatic improvement. Grade 3 toxicities were observed in 19 (58%) patients. In another report [113], four SM patients (all *KIT*D816V positive; two with ASM, one SM-AHNMD, and one ISM) were treated with dasatinib at a dose ranging from 50 mg to 100 mg twice daily. Two patients (eight each with ASM and SM-AHNMD) had a major response, which in the case of the SM-AHNMD patient was accompanied by decrease in the BM MC burden. Both responders experienced an initial exacerbation of MCMRS and rash lasting several days before the benefits of dasatinib therapy became evident.

   Summary: Dasatinib appears to have modest activity in KITD816V-positive SM. The cumulative published experience to date does not clarify as to which group of SM patients is likely to obtain the most benefit from dasatinib therapy.

   (ii) Midostaurin (PKC412) has in vitro activity against kinase domain KIT mutants (D816Y and D816V) [94,114], and treatment of a patient with MCL who harbored *KIT*D816V resulted in transient clinical benefit [115]. In a recent phase-2 study PKC412 was orally administered to 26 SM patients at 100 mg BID [116]. SM variants included ASM (n = 4), SM-CMML (n = 14), SM-MDS (n = 3), SM-MDS/MPN-U (n = 1), and MCL (n = 4). Major response rate per conventional criteria was 38%. Major responses included normalization of hypoalbuminemia, improvement of hemoglobin and platelet counts, resolution of liver function abnormalities, improvement of pleural effusion and ascites, and reversion of weight loss. Some of these responses were accompanied by improvement in hepatosplenomegaly, a $>$50% decrease in serum tryptase level and/or BM MC burden, and improvement in MCMRS. One patient with MCL had achieved a near complete remission with a decrease of serum tryptase from 763 to $<$20 ng/mL, and decrease of marrow MC burden from 60–70% to 5%. The most common drug side effects were nausea, vomiting, diarrhea, and fatigue. Asymptomatic hyperlipasemia occurred in five patients. Treatment had to be discontinued in 18 (69%) patients.

   Summary: PKC412 has activity in SM and might produce substantial reduction in MC burden in some patients. However, it is currently not clear which patients with SM stand to benefit from such treatment and more studies are needed to clarify the

advantage of PKC412 over treatment with IFN-α or cladribine, which are currently considered first line treatment in ASM or symptomatic indolent SM.

(iii) Masatinib mesilate (AB1010) has been shown to inhibit human and murine KIT with juxtamembrane activating KIT mutations, as well as PDGFRA-α/β, and Lyn kinases at nanomolar concentrations in cell-based assays [117]. In contrast, masatinib only weakly inhibited KITD816V-driven cell proliferation (micromolar concentrations). Masatinib was administered to 25 patients with symptomatic cutaneous or ISM that was refractory to conventional therapy, and where *KIT*D816V was absent in at least one MC infiltrated organ (skin or BM) [118]. Patients were randomized to receive 3 or 6 mg/kg/day for 12 weeks; the primary endpoint was change in symptoms at week 12 relative to baseline. There was a significant improvement in frequency of flushing, pruritus score, and Hamilton rating for depression by 64%, 36%, and 43%, respectively. The overall clinical response (≥50% improvement in baseline symptom without deterioration or emergence of another symptom) was 56%. Twenty-two patients (88%) completed the study; two discontinued due to adverse events (AE). In the initial 12-week phase, 21 patients (84%) experienced at least one masatinib-related AE (mild [$n = 11$], moderate [$n = 19$], and severe [$n = 9$]). The most common AE were nausea/vomiting (52%), edema (44%), muscle spasms (28%), and rash (28%). One patient developed masatinib-related agranulocytosis that was reversible. Seventeen patients (68%) entered the extension phase and at the time of publication, eight patients (32%) were still receiving treatment. In another report of 35 ISM patients (22 and 2 patients with mild-moderate and severe depression, respectively), depression scores were significantly improved (20% improvement in initial score) in 67% of cases after masatinib therapy for 12 weeks [119].

Summary: Given its lack of activity against *KIT*D816V, masatinib appears to be at a disadvantage as compared with other "targeted" therapies for the treatment of adult SM. In the absence of a head-to-head trial, it is unclear if masatinib has any clear advantage over imatinib for the treatment of symptomatic ISM. The frequency of AE in the former study was relatively high, which likely explains why the QLQ-C30 symptom score showed little improvement as compared with baseline.

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